REMARKS

Claims 1-11, 15-33 and 37-40 are pending in this application. Claims 1-11, 15-33, and 37-40 are rejected. By the present amendment claims 1, 5, 6, 15, 16, 17, 18, 19, and 40 are amended for clarity. In addition, claims 2-4, 7-11, 20-33 and 37-39 are hereby canceled without prejudice or disclaimer, and new claims 41 and 42 are hereby added. Support for the amended and new claims are found in paragraphs 7, 21, 25, 26, 29, 38 and elsewhere of the present divisional application. Thus, the amendments and new claims add no new matter.

In view of the amendments and following remarks, reconsideration of claims 1, 5, 6, 15-19, and 40 and consideration of new claims 41 and 42 are respectfully requested.

Compliance With CFR 1.821(a)-(d)

As the patent office has requested, applicants are submitting herewith a computer readable form (CRF) copy of the sequence listing for the present application. The sequences in the CRF are the same as the sequences in the paper copy of the sequence listing submitted to the patent office with the instant application and thus add no new matter.

Claim Rejection -35 USC § 112, First Paragraph

Claims 1-3, 6, 7, 9, 10, 15-18, 20-22, 25, 26, 28, 29 and 31-33 are rejected under 35 USC § 112, first paragraph, "as failing to comply with the written description requirement." (See Page 4 of the Office Action.)

Claims 2, 3, 7, 9, 10, 20-22, 25, 26, 28, 29, and 31-33 are canceled rendering the rejection of these claims moot. Claim 1 has been amended to recite that the transgenic animal is a mouse and that the promoter of the transgene is either a human FGF1B promoter or a mouse FGF1B promoter. Applicant submits that claim 1 as amended meets the written description requirement of § 112, first paragraph. Claims 6 and 16-18 depend from claim 1 and also meet the written description requirement. Claim 15, as amended, recites a method of identifying drugs that are effective at inhibiting growth of the brain tumor of the transgenic mouse of claim 1 by administering candidate drugs to the transgenic mouse of claim 1. One of ordinary skill in the art would understand and appreciate that applicant was in possession of the method of claim 15 at the time the present application was filed. Accordingly, Claim 15 meets the written description of 35 USC §112.

Claims 1-11, 15-33 and 37-40 are rejected under 35 USC §112, first paragraph. The Patent Office stated: "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to practice the invention commensurate in scope with these claims." (See Pages 8 and 11 of the Office Action.)

Claims 2-4, 7-11, 20-33 and 37-39 have been canceled rendering the rejection of these claims moot. Claim 1 has been amended to recite that the transgenic animal is a mouse and that the promoter is either the human FGF1 B promoter or the mouse FGF1 B promoter. Applicant has provided the sequences of such promoter. Moreover, applicant has produced three families of transgenic mice that comprise brain tumor cells that do not express glial fibrillary acidic protein, S-100, synaptophysin and neuron-specific enolase by incorporating a transgene comprising nucleotide -540 through nucleotide +31 of the human FGF1B operably linked to a sequence that encodes the SV40 T antigen into the cells of such transgenic mice. In view of the results achieved and reported by Applicant, it would not require undue experimentation for one of ordinary skill in the art to produce mice that have such brain tumor cells using either a human or a mouse FGF1B promoter operably linked to a sequence encoding an SV40 large T antigen as recited in amended claim 1. Accordingly, Applicant submits that the transgenic mouse of claim 1 is fully enabled. In addition, claims 5, 6 and 16-18 all of which depend from claim 1 are also enabled.

With respect to claim 15, the Patent Office stated:

> No working examples describing the particulars of the claimed method are disclosed. The claimed method encompasses comparing the growth of tumors between treated and untreated mice. However the specification teaches that even within the transgenic mice that were constructed the only highly reproducible location of tumor growth was in the caudal pons,.....Further the mouse lines showed marked variation in the distribution and size of tumors within the central nervous system....Therefore it would be impossible to predict whether the differences in the grown of tumors between <u>different</u> transgenic mouse lines was due to drug or variations in construct expression.
>
> ...
>
> The specification does not provide any guidance on the molecular size of the drugs to be administered or the route of administration of the drug. Padridge et al. teaches that the blood brain barrier formed by the capillary endothelium excludes 100% of large molecule therapeutics and more than 98% of all small-molecule drugs {Padride et al. (2005) Neurorx.2:3-14}. (See Page 9 of the Office action, emphasis added.)

Respectfully, working examples are not required to meet the enablement requirement of §112. All that is required is that the specification provide sufficient guidance that one or ordinary skill in the art can practice the claimed invention without undue experimentation. Moreover, one of ordinary skill in the art would not compare tumor growth in mice from different lines. In comparing the effect of treatment with drug and no drug, one of ordinary skill in the art would use matched animals, i.e., mice from the same transgenic line. Furthermore, it is known in the art that the capillary endothelium in tumor tissue provides less of a barrier to blood borne drugs than the capillary endothelium in normal brain tissue as discussed in Padridge et al., which is directed to studies on CNS disorders rather than brain tumors Finally, contrary to the patent office's assertion as to lack of guidance regarding routes of administration, applicant has indicated that the candidate drug could be administered intravenously, intradermally, or intracerebrally. (See paragraph 38 of the present application.) In view of what is known in the art and taught in the present application, it would require nothing more than routine experimentation for one of ordinary skill in the art to practice the method of claim 15. Accordingly, claim 15, as amended, is enabled.

35 USC § 103 Rejection

Claims 12 -14 and 37 are rejected under 35 U.S.C. § 103 as being unpatentable over Alam et al. (The Journal of Biochemistry. Vol. 271:30263-30271, 1996)(hereinafter "Alam et al.") or Ray et al. (The Journal of Biochemistry. Vol. 272: 7456-7555, 1997)(hereinafter Ray et al.) in view of Takahashi et al. (Exp. Anim. 48: 255-261, 1999) (hereinafter "Takahashi et al.") and Perraud et al. (Oncogene Vol. 7: 993-997, 1992) (hereinafter "Perraud et al.")

None of the primary or secondary references applied by the Patent Office, either alone or combined, teach or suggest that one could obtain a transgenic mouse comprising brain tumor cells that do not express glial fibrillary acidic protein (GFAP), S-100, synaptophysin and neuron-specific enolase by employing a transgene that comprises a human or mouse FGF1B promoter operably linked to a sequence encoding the SV40 large T antigen as recited in claim 1 as amended. Moreover, upon reading these references, one of ordinarily skill in the art would not reasonably expect that such a mouse could be produced.

Alam et al. merely recites the sequence of the mouse FGF1 B promoter and that "FGF-1 message and its protein appears to be largely neuronal, with little or no glial component", and

"that high levels of FGF-1B transcript occur in glioblastomas and glioblastoma-derived cell lines." (See page 30270, second full paragraph in column 2 of Alam et al.) The brain tumor cells of the transgenic mouse of claim 1 do not express GFAP and thus do not have the characteristics of a gliobastoma. Moreover, unlike the neuronal cells discussed in Alam et al., the tumor cells of the transgenic mouse of claim 1 do not express FGF1. (See paragraph 51 and Figure 7E of the instant application.) Thus, any teachings in Alam et al. about the types of cells that express FGF1B would not lead one of ordinary skill in the art to expect that one could produce a transgenic mouse having brain tumor cells that do not express GFAP, S-100, synatophysin and neronal specific enolase using the transgene recited in claim 1 as amended.

Ray et al. recites constructs with portions of the FGF1B promoter linked to a nucleotide sequence that encodes luciferase. Ray et al. also provides information about the activity of these constructs in glioblastoma cells. Ray et al., however, does not teach or suggest that one could produce a transgenic mouse comprising brain tumor cells that do not express GFAP, S-100, synatophysin and neronal specific enolase by replacing the luciferase encoding sequence with a sequence encoding the SV40 T antigen. Ray et al does not teach or suggest that such a modification would be desirable. Moreover, Ray et al. does not teach or suggest that such animal could be produced.

Takahasi et al. does not provide the motivation that is absent from Ray et al. or Alam et al. The transgene of Takahasi et al. includes an SV40 T-antigen promoter. (See page 256, last full paragraph of the Introduction of Takahasi et al.) The transgene of Takahasi et al. does not include a tissue specific promoter, much less the FGF1 B promoter. Moreover, the transgene of Takahashi et al. does not include a sequence that encodes the SV40 large T antigen. The transgene of Takahasi et al. comprises a sequence that encodes the temperature sensitive (ts) mutant of the SV40 T antigen. (Id.) Thus, even if one were to combine the FGF1 B promoter of claim 1 with the coding sequence in the transgene of Takahasi et al., one still would not obtain the transgene recited in claim 1 as amended. Lacking a transgene that comprises either a tissue specific promoter or the coding sequence of the SV40 T antigen, Takahasi et al., alone or combined with Alam et al. and Ray et al., would not cause one of ordinary skill in the art to reasonably expect that the transgenic mouse of claim 1 could be produced..

Perraud et al, also, would not motivate one of ordinary skill in the art to prepare a transgenic mouse comprising brain tumor cells that do not express GFAP, S-100, synatophysin

and neronal specific enolase by using a transgene comprising a mouse or human FGF1B promoter operably linked to a sequence encoding the SV40 large T antigen as recited in claim 1, as amended. Perraud et al. recites a cystic fibrosis membrane conductance regulator (CTFR) promoter-SV40 T antigen fusion transgene, and transgenic mice comprising such a transgene. Perraud et al. indicates that the authors "expected that such an approach would permit the development of lung, pancreas and gastrointestinal epithelial tumors." (see, page 993, next to the last pargraph of column 2 of Perraud et al.) However, "surprisingly", the authors did **not** obtain such tumors. Id. Moreover, Perraud et al. provides at least four different possible reasons as to why the authors failed to detect SV40 T antigen protein in tissues such as the lungs and pancreas of the transgenic animals that they had produced using their transgene. (See bridging paragraph on page 996 of Perraud et al.) Thus, Perraud et al. clearly shows the unpredictability in the transgene art, particularly in transgenes containing a sequence encoding the SV40 large T antigen. As a result, one of ordinary skill in the art, upon reading Perraud et al., either alone or in combination with Ray et al. and Alam et al., would have no reason to believe that introduction of a transgene comprising an FGF1 B promoter operably linked to a sequence encoding the SV40 large T antigen would lead to a mouse comprising brain tumor cells that have the characteristics recited in claim 1, as amended. In other words, Perraud et al. would not lead one of ordinary skill in the art to believe that the transgene recited in claim 1 as amended would achieve such results.

In making the current rejection, the Patent Office has selected and combined the promoters recited in Alam et al. and Ray et al. with a sequence encoding an SV40 large T antigen, a coding sequence that is found in the transgene of Perraud et al. However, to sustain a §103 rejection, it is not enough that one may modify a reference in view of a second reference. The modification cannot be considered obvious unless at least one of the prior art references suggests the desirability of the modification. Obviousness can not be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.

Claim 1, as amended, recites a transgenic mouse comprising brain tumor cells that do not express GFAP, S-100, synatophysin and neronal specific enolase. Such a mouse is not suggested by the applied references. One of the references applied by the patent office, namely Takahasi et al. does not recite an FGF1B promoter **OR** a sequence encoding the large SV40 T antigen.

Another applied reference, Perraud et al, suggests that combining a sequence encoding the SV40 large T antigen with the tissue specific promoter, namely the CFTR promoter, leads to unexpected results, for which there are multiple possible but uncertain explanations. Neither Alam, et al. nor Ray, et al. overcomes the unpredictability suggested by Perraud et al., i.e., that unexpected results occur when sequences encoding the SV40 large T antigen are operably linked to tissue specific promoters. Thus, the references applied by the Patent Office do not support its position. Lacking such support, the § 103 rejection is improper and should be withdrawn. rejection is improper and should be withdrawn.

In view of the amendments and remarks, Applicant submits that claims claims 1, 5, 6, 15-19, and 40 and new claims 41 and 42 are now in condition for allowance. Prompt notice of such allowance is respectfully requested.

Respectfully submitted,

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